Uveitis and systemic disease

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Abstract

A prospective study was conducted of 865 patients with uveitis to determine the frequency of associated systemic diseases and to assess the value of limited laboratory screening of these patients. All patients underwent a standard diagnostic protocol followed - when indicated - by special tests and procedures performed in order of likelihood ('tailored approach'). For 628 patients (73%) a specific diagnosis was established based on history, ophthalmologic examination, and laboratory and radiographic studies. A definite association with systemic disease was determined for 220 patients (26%). A relationship with a subclinical systemic disorder could be presumed in 201 cases (23%) and a well-established clinical uveitis entity without a recognisable systemic disorder was present in 207 cases (24%). For 237 patients (27%) a diagnosis could not be determined. The most frequently observed systemic diseases were sarcoidosis (7%) and HLA-B27-associated seronegative spondylarthropathies (6%). Presumed or definite toxoplasmosis was encountered in 10% of cases. HLA-B27-associated acute anterior uveitis was the most common clinical entity (17%). In the majority of cases the presence of a systemic disease was not suspected prior to eye involvement and was only recognised after the subsequent diagnostic procedures.

Uveitis is a general term for inflammation of the uveal tract due to any cause and usually includes a large group of diverse diseases affecting not only the uvea but also the retina and vitreous. The aetiology is difficult to establish since the exact cause of uveitis frequently remains unknown.

Therefore the current International Uveitis Study Group classification system is based on the anatomical location of the inflammation: anterior uveitis (iris and ciliary body), posterior uveitis (choroidea and retina), intermediate uveitis (peripheral retina and pars plana of the ciliary body), and panuveitis (generalised inflammation of the whole uvea).[1] The differential diagnosis for uveitis depends on the type of uveitis involved and various geographical, environmental, and population factors; moreover it continues to change as new entities are recognised and improved diagnostic techniques become available.[2]

Uveitis is not a single disease but includes ocular involvement related to various systemic disorders as well as primary ocular conditions. The association of uveitis and systemic disease is well known. In earlier studies the majority of cases were attributed to tuberculosis and syphilis whereas recent reports show an association with various generalised diseases.[2-10]

We conducted a prospective study to assess the frequency and type of systemic diseases associated with intraocular inflammation using a standard diagnostic evaluation in a large group of patients.

Patients and methods

The study included 881 consecutive patients with uveitis who visited the Ophthalmologic Department of the Academic Medical Centre in Amsterdam between 1984 and 1989. Sixteen patients were not available for follow-up; therefore 865 uveitis patients could be evaluated. AIDS patients were not included in this study. Our institution combines secondary and tertiary ophthalmic care: patients are referred by ophthalmologists from a large area and also by general practitioners from a smaller local area.

Complete ophthalmic examination was performed in all cases. The assessment included a visual acuity test, slit-lamp examination, indirect funduscopy, posterior pole evaluation with a 90 dioptre lens, and intraocular pressure measurements. The results of the ophthalmic and laboratory examinations were stored in a computer databank.

The diagnostic criteria for uveitis were those laid down by the International Uveitis Study Group.[1] The diagnostic category intermediate uveitis describes the anatomical position of an intraocular inflammation. A (classic) subset of intermediate uveitis with the inflammatory focus in the peripheral retina and cystoid macular oedema without evidence of general disease was called pars planitis.

All patients underwent a standard screening protocol depending on the ophthalmic anatomical classification (Table 1). Selected patients (depending on the history, character and activity of their ocular disease, as well as the outcome of the laboratory and radiographic screening procedures) underwent special tests and diagnostic procedures ('tailored approach'). These tests included HLA-A29 and HLA-B5 typing, radiography of the sacroiliac joints and

Table 1 Screening of uveitis patients

	Anterior uveitis	*Intermediate and posterior uveitis*	*Panuveitis*
ESR, red and white blood cell count, glucose	+	+	+
HLA-B27	+	−	+
Angiotensin converting enzyme, lysozyme	+	+	+
Lues serology	+	+	+
Antinuclear antibodies*	+	−	+
Chest radiography	+	+	+

*Only in children under 16 years.

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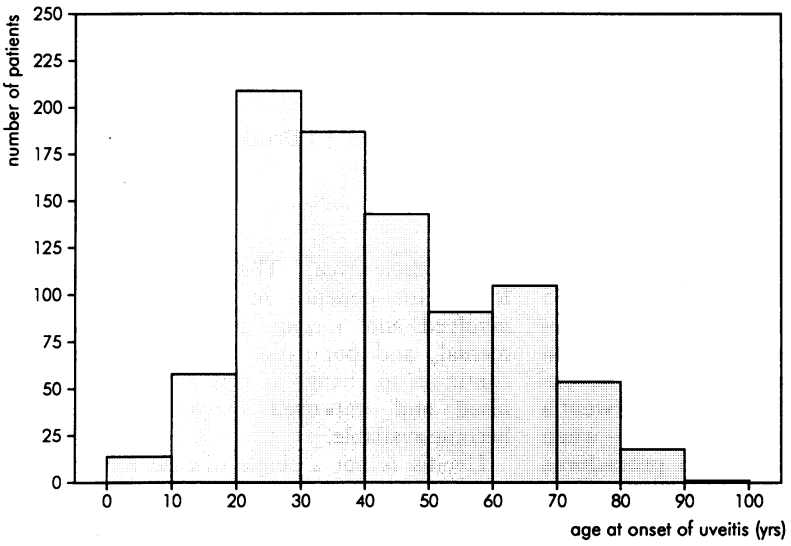

Figure 1 Age at onset of uveitis.

skull, computed tomographic (CT) brain scanning, gallium-67 whole body scintigraphy, conjunctival and lacrimal gland biopsy, Mantoux test, and aqueous humour analysis for evidence of intraocular synthesis of specific antiparasitic and antiviral antibodies.

The diagnosis of presumed ocular toxoplasmosis was based on the clinical observation of unilateral focal necrotising retinitis sometimes associated with typical old pigmented scars. *Toxoplasma* serology was not routinely performed since anti-toxoplasmal antibodies are present in the majority of the Dutch population, therefore positive titres in adults have no diagnostic value.[11] In doubtful cases the intraocular production of anti-toxoplasmal antibodies was assessed by aqueous humour analysis (Goldmann-Wittmer Coefficient).[12] Radiography or CT scanning of the skull was performed only when patients with ocular toxoplasmosis had neurological symptoms. Systemic toxoplasmosis was diagnosed in the event of clinical evidence of extraocular involvement. The diagnosis of acquired ocular toxoplasmosis was based on the presence of focal necrotising retinitis and a more than four-fold rise of the antibody titre together with specific IgM antibodies in the circulation. Congenital toxoplasmosis was the established diagnosis for neonates with focal retinitis and positive serological findings.

The diagnosis of sarcoidosis was always confirmed by histological examination of biopsy specimens. Depending on the signs of the disease a biopsy was obtained from lungs, peripheral or mediastinal lymph nodes, conjunctiva, lacrimal gland, or liver. When none of these organs were clinically involved the biopsy was not attempted. We did not perform the Kveim test. Presumed ocular sarcoidosis was diagnosed when uveitis patients had chest radiographic or gallium-67 scintigraphic patterns typical of sarcoidosis and/or increased serum levels of angiotensin-converting enzyme (above 60 U/l)[13] without however histological evidence of the disease.

All HLA-B27 positive patients with anterior uveitis who had complaints of the peripheral joints or low back pain were examined by the rheumatologist. The diagnosis of ankylosing spondylitis was established when the patients fulfilled the criteria described by Bennet and Burch.[14] The criteria proposed by Lee *et al* were used for the diagnosis of Reiter's syndrome.[15]

All other systemic diseases were diagnosed according to current diagnostic criteria; the patients were also examined by the respective specialists.

We used the χ^2 test for statistical analysis; $p<0{\cdot}01$ was considered significant.

Table 2 Classification of uveitis patients according to anatomic position

	No	*%*
Anterior uveitis	471	54·5
Intermediate uveitis	76	9·0
Posterior uveitis	142	16·5
Panuveitis	176	20·0
Total	865	100

Table 3 Systemic disease in uveitis patients

	All uveitis patients (n=865)	*Anterior uveitis (n=471)*	*Intermediate uveitis (n=76)*	*Posterior uveitis (n=142)*	*Panuveitis (n=176)*
Systemic disease	220	118	8	34	60
Sarcoidosis	59	23	3	8	25
Seronegative spondylarthropathies	48	44	0	0	4
Diabetes mellitus*	20	20	0	0	0
Tuberculosis	12	6	0	2	4
Toxoplasmosis with extraocular manifestations	9	0	0	7	2
Juvenile rheumatoid arthritis	8	8	0	0	0
Behçet's disease	7	0	0	1	6
Lues	6	5	0	0	1
Multiple sclerosis	6	0	4	0	2
Miscellaneous	45	12	1	16	16
Presumed systemic disorder	201	110	4	67	20
HLA-B27 associated, without rheumatic disease	105	105	0	0	0
Presumed ocular toxoplasmosis	74	0	0	62	12
Presumed ocular sarcoidosis	22	5	4	5	8
Specific ocular disease†	207	88	52	19	48
Undetermined	237	155	12	22	48

*Diabetes mellitus in nine additional patients was considered not related to their uveitis.
†See Table 4.

Results

The mean age at onset of uveitis was 42 years (range 3–91 years). The peak age of onset of uveitis occurred in the third and fourth decades; 45% of our series presented between 20 and 40 years of age (Fig 1). The male:female ratio was 1:1 for the entire series as well as for all anatomical categories of uveitis. Our study included 83 (10%) black patients (the country of origin being mainly Surinam), 38 (4%) oriental patients (predominantly from Indonesia) and 40 (5%) patients from the Mediterranean Basin.

In this series anterior uveitis was the predominant clinical type (471 cases, 54·5%); 176 (20%) patients presented with panuveitis, 142 (16·5%) with posterior uveitis, and 76 (9%) with intermediate uveitis (Table 2).

The specific diagnosis for our patients with uveitis is shown in Table 3. For 220 (26%) of the 865 patients the intraocular inflammation was considered to be causally related to the systemic disease. Systemic diseases most frequently associated with uveitis included sarcoidosis (59/865; 7%) and HLA-B27 associated seronegative spondylarthropathies (48/865; 6%). Syphilis and tuberculosis were responsible for 0·6% (6/865) and 1·4% (12/865) of all cases respectively. Toxoplasmosis with clinical extraocular mani-

Table 4 Specific ocular diseases among uveitis patients

	All uveitis patients (n=207)	*Anterior uveitis (n=88)*	*Intermediate uveitis (n=52)*	*Posterior uveitis (n=19)*	*Panuveitis (n=48)*
Fuchs' heterochromic cyclitis	53	30	0	0	23
Pars planitis	52	0	52	0	0
Idiopathic vasculitis	19	0	0	14	5
Viral uveitis*	39	24	0	2	13
Posner-Schlossman syndrome	8	8	0	0	0
Miscellaneous	36	26	0	3	7

*Included are cases with herpes zoster uveitis (clinical diagnosis), herpes simplex and Epstein-Barr virus uveitis (proven by aqueous humour analysis), and eight patients with acute retinal necrosis.

festations comprised 1% (9/865) of the series, whereas presumed toxoplasmosis accounted for 9% (74/865). For 12 patients the diagnosis of definite congenital toxoplasmosis could be confirmed. Acquired ocular toxoplasmosis was observed in four patients all of whom were receiving immunosuppressive drugs during the onset of uveitis (three patients for various malignancies and one after renal transplantation).

In 201 (23%) cases a systemic disease was presumed without however, the clinical evidence of extraocular involvement required for diagnosis. The HLA-B27-positive acute anterior uveitis patients who did not fulfil the criteria required for the diagnosis of ankylosing spondylitis and patients with presumed congenital toxoplasmosis or sardoidosis were included in this group.

For 207 (24%) patients a specific ocular disease was diagnosed without an underlying systemic disorder and included 53 (6%) patients with Fuchs' heterochronic cyclitis and 52 (6%) patients with classic pars planitis (Table 4). In the remaining 237 (27%) cases uveitis was not associated with a systemic disorder but was also not characteristic of a recognised type of uveitis.

Among patients with anterior uveitis HLA-B27-associated acute anterior uveitis was the most frequently diagnosed entity (149/471; 31%) with a male predominance (male:female ratio was 1·4:1, $p<0·05$). Anterior uveitis was considered to be related to diabetes mellitus in 4·3% of patients.[16] In nine additional patients diabetes mellitus was observed although another aetiology was established for the uveitis. Miscellaneous systemic diseases in patients with anterior uveitis included gonorrhea, schistosomiasis, lepra, loiasis, ornithosis, and leukaemia.

Eight of 76 (10·5%) patients with intermediate uveitis had a recognisable systemic disease (four had multiple sclerosis, three sarcoidosis and one Lyme borreliosis). Pars planitis with peripheral vitreous opacities and snowbanking without evidence of systemic disease was observed in 52 (68%) of 76 patients with intermediate uveitis.

Toxoplasmosis (systemic and presumed ocular) was the most frequently diagnosed disease in the posterior uveitis group (69/142 patients, 49%) whereas sarcoidosis was more common in the panuveitis group (biopsy proved and presumed; 33/176 patients, 19%). Miscellaneous diseases in the posterior and panuveitis groups included autoimmune diseases such as systemic lupus erythematosus, mixed connective tissue disease, Wegener's disease, essential cryoglobulinaemia as well as Vogt-Koyanagi-Harada syndrome, subacute sclerosing panencephalitis, candidiasis, toxocariasis, and Lyme borreliosis.

Of the seven Behçet patients, five were from the Mediterranean Basin ($p<0·001$) and of the 59 patients with sarcoidosis 22 (37%) were black ($p<0·001$).

Fifteen of 59 (25%) patients with biopsy-proved sarcoidosis were known to have this disease before the onset of uveitis; for 44 (75%) patients the diagnosis was established after the onset of uveitis. In five cases initial screening for sarcoidosis was negative and the diagnosis was not proved until more than 1 year after the onset of ocular symptoms.

The diagnosis ankylosing spondylitis was established before the onset of uveitis for 16 of 41 (39%) patients; for the remaining 25 (61%) patients the diagnosis was made during the uveitis work-up. Of seven patients with Reiter's syndrome three were known to have this disease before the onset of uveitis.

Discussion

In this prospective study of 865 patients the specific diagnosis for an intraocular inflammation was established in 73% of all cases. Systemic disease, which could be considered to be causally related to the intraocular inflammation, was diagnosed in 26% of all cases on the basis of the standard initial screening protocol followed by a 'tailored' diagnostic approach. In an additional 23% of all cases the presence of a systemic disorder was presumed. The majority of our patients were not known to have systemic disease prior to the ocular symptoms and the diagnosis was not established until the uveitis work-up.

The reported frequency of a systemic disease underlying uveitis in the last two decades varies from less than 19% to 46%.[2 6-8 10 17] The study with the lowest frequency involved 120 new uveitis patients from northern Finland predominantly with anterior uveitis (88%); there was no specified diagnostic protocol and the aetiological factors studied were mainly of infectious origin.[17] The highest frequency of systemic disease was found for 368 uveitis patients in hospital in London (58% had anterior uveitis); ocular toxoplasmosis, the most common entity, was classified as a systemic disorder.[6] In a report of 236 patients with uveitis who were referred for a medical examination to an internist, Rosenbaum found systemic disease in 40% of patients; the highest frequency was found for Reiter's syndrome (7·2%) followed by sarcoidosis (5·5%) and ankylosing spondylitis (5·5%).[10] The extensive series of Henderly *et al* included a retrospective analysis of 600 referred patients 22% of whom had systemic disease (patients with toxoplasmosis were not included; 7%); 4% had sarcoidosis.[2]

Comparison of uveitis statistics from various countries is very difficult. A large survey comparing the pattern of uveitis in London and Iowa revealed no major differences (histoplasmosis was excluded).[7] In another series of 240 Chinese patients with uveitis Behçet's disease was responsible for 18% of all cases.[18]

Several factors may contribute to the variation in reported incidence of the various systemic diseases underlying intraocular inflammation. The true geographical differences as well as the selection of patients, author's interest, diverse

diagnostic investigations, and criteria influence the results of the studies. Most published reports are retrospective and concern only those patients in hospital or otherwise selected. The racial and age distributions are not always specified and the laboratory tests for uveitis patients are usually not consistent. Another potentially important factor that could play a role in the reported discrepancies are the criteria used for diagnosis of the specific systemic disease. The fact that our hospital is in part a referral centre helps to explain the bias of the present study.

In addition the reported incidence of various diseases may be distorted due to confusion about the nomenclature used for uveitis patients. The descriptive anatomical classification system and the aetiological diagnosis are frequently used together in a single coding system which is not correct in our opinion. An anatomically defined uveitis entity (for example anterior uveitis) may include different causes and associations (lues, viral infection, sarcoidosis, ankylosing spondylitis, Reiter's syndrome, and so on) while the aetiological diagnosis does not always indicate the localisation of the inflammatory process. The descriptive and aetiological approaches do not exclude one another and in our view should be used separately as we have done in this present series.

In this study the anatomical entity most frequently associated with definite systemic disease was panuveitis (34%) followed by anterior uveitis (25%). Anterior uveitis was reported by Rosenbaum to be the one most likely to be associated with systemic disease (53%);[10] however other studies do not confirm this high rate of association.[2 8 17] These differences were attributed to the different referral patterns which lead to different representations of the various types of uveitis. In our study 25% (118/471) of patients with anterior uveitis had systemic disease (predominantly ankylosing spondylitis) and 22% patients (105/471) with acute anterior uveitis were HLA-B27 positive without a well defined associated systemic disease (Table 3). Although many of the latter had complaints suggesting related rheumatic disease they did not fulfil the required diagnostic criteria.

The most frequently observed systemic disease among our uveitis patients was (histologically proved) sarcoidosis (7%); this percentage is somewhat higher than that reported in previous studies. The higher frequency of sarcoidosis found in this study could be explained by our systematic assessment of both angiotensin-converting enzyme and lysozyme levels as well as chest x rays in all cases followed by examination of biopsy specimens when sarcoidosis was suspected.

The differential diagnosis for uveitis continues to change. Recently Lyme borreliosis was found to cause diverse ocular symptoms including scleritis, vitritis, retinitis, and papillitis.[19 20] The two patients with ocular Lyme borreliosis in our series were diagnosed during the last year of the study; however a systematic search for this disease was not carried out in the preceding years. The exact frequency of Lyme disease among patients with intraocular inflammation is not yet known.

The search for a systemic disease in patients with uveitis is a controversial subject. It is generally agreed that extensive unfocused laboratory screening is inefficient and very costly and that a patient with uveitis who has general medical examination will undergo physical and laboratory examinations which will not contribute to the correct diagnosis of the disease underlying the uveitis.[21] In this study we used a limited screening protocol based on the anatomical classification of the uveitis and systemic diseases that could cause the intraocular inflammation. Subsequent diagnostic procedures were planned depending on the suspected diagnosis. This 'tailored' approach demands that a precise history be taken and careful examination be performed.

The changing pattern of uveitis due to the eradication of various diseases and the recognition of new diseases and advance in diagnostic techniques implies a change in the diagnostic approach to uveitis. Laboratory tests performed with peripheral blood from patients with intraocular inflammation may not be discriminatory. For infectious types of uveitis negative blood test results can sometimes be used to exclude the suspected diagnosis but one may not conclude that a specific disease is the cause of an ocular ailment when peripheral blood yields a positive test result.[21] The aqueous or vitreous analysis is therefore becoming indispensable especially for the infectious types of uveitis.

In this prospective study we established a specific diagnosis for the majority of uveitis patients, 26% of whom had a definite systemic disease; for an additional 23% of patients a relationship with a subclinical systemic disorder could be presumed. To obtain such a diagnosis a complete ophthalmic examination with a detailed history and the 'tailored' diagnostic approach are essential.

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FIFTY YEARS AGO

Phlyctenular ophthalmia

It is concluded that phlyctenular ophthalmia is a manifestation, not of tuberculous disease, but of tuberculous infection, the phlycten making its appearance only when a hyperallergic phase is present and there is a suitable (? specific) exciting factor of endogenous or exogenous origin. It is suggested that the age distribution, sex-incidence and seasonal variation seen in phlyctenulosis are best explained on the assumption that the affection is tuberculous in character. The prognostic significance of the phlycten is graver than that of a positive tuberculin reaction in a child; this is borne out by the subsequent incidence of tuberculosis and mortality from it in children previously affected with phlyctenulosis. – From 'The aetiology of phlyctenular ophthalmia,' by Arnold Sorsby. *Br J Ophthalmol* 1942; 26: 211.